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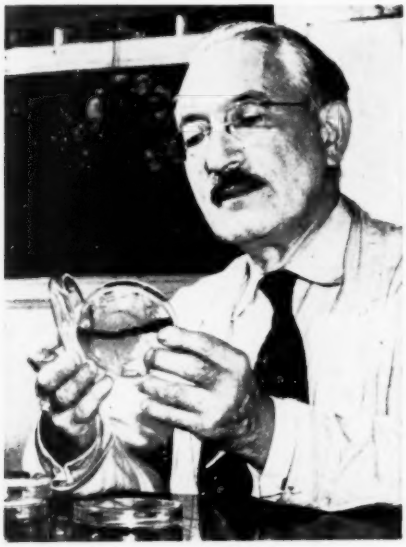

DR. SELMAN A. WAKSMAN

Recipient of the 1949 Research Award of the American Pharmaceutical Manufacturers' Association.

Since 1825 *June, 1949*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $3.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 30 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

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AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 121 JUNE 1949 No. 6

CONTENTS

E D I T O R I A L

THE BRITISH DILEMMA

THE economic crisis in England is of far greater moment and significance than most Americans recognize. Nothing, other than our own economic collapse, could cause more widespread repercussions than the failure of Britain's economy. Pharmacists may wonder in what way this is germane to the practice of pharmacy but it is as we shall try to demonstrate.

First we should understand several unmistakable facts. Foremost of these is that the fate of Britain is unalterably attached to our own and ours to hers. History has proved that our two countries cannot be dissociated and this fact must be accepted even by the most outspoken critics on both sides of the Atlantic. Second, Britain, as a result of having withstood the German force almost alone until we were prepared, vitiated her economic wealth and reserves almost to the point of extinction. Third, whether by choice or necessity, the British colonial empire is almost dissolved leaving England with only her own resources on which to depend. These facts are clear cut and all contribute in a major way to the extremely low standard of living endured by the English people. This is not, however, the answer to the recent failure of England to improve her economic position and to build up dollar reserves which she must have if she is to maintain even the *status quo*.

The United States has given billions of dollars to help European recovery and England has received a major portion of these funds. We are in full sympathy with the Marshall plan and it was entirely appropriate that England receive such financial support. We are, however, distressed to learn that, while all other countries receiving Marshall plan aid are showing substantial progress, England has dissipated her dollars with little economic progress to show for them. Already she has announced her intention of returning to bilateral trade agreements with other nations. This is in direct conflict with the principle of multilateral trade upon which

the peace and future of Western Europe depends. If trade and currency restrictions again are to return on the European scene we can expect economic strangulation and then war to follow. The leaders of Britain must know this and we are aghast that they seek this means of economic relief rather than a change in domestic policy which would be far less dangerous to world stability. Up until now, Americans have been tolerant of the British labor government, although its domestic policies are quite foreign and distasteful to those of us who dislike socialistic planning and its required regimentation. Until now, Americans did not feel that they had a right to protest. Quite frankly, however, many Americans winced when they were required to pay taxes to support a government dedicated to theories and principles that are utterly repugnant to the majority in this country. That we have done this until now without complaint is some tribute to our sincere desire for the peace and prosperity of our English brothers.

The time has now come when we must in all fairness ask whether the labor government in its eagerness to socialize industry and to provide all manner of benefits for the worker in the welfare state that is Britain has not overlooked the cost of such a program? Can the government maintain this Utopian state for long without economic collapse? It would appear not since the costs of production in England must be lowered if its goods are to compete in world markets with those made in other countries.

It is our opinion that government ownership and operation in industry raises costs when all elements are considered. Those industries which are not state owned are so heavily taxed to support the welfare state that initiative is destroyed and modernization of equipment is impossible. There is also considerable waste in such systems as the British Health Plan where malingering is bound to increase and much more service demanded than is needed. It is an inescapable fact that when total security is afforded the worker no challenge remains and his productivity drops. Those who look for state control of the means of production, regimentation of the worker, and a social state as the best means for guaranteeing a high standard of living and human happiness are to be bitterly disappointed.

When man is given all these things he inevitably develops a mental stagnation together with a docile acceptance of his fate and

the bleakness of his future. There is a touch of God in every man that makes it necessary for life to be an exciting adventure and one filled with challenge, albeit some risk. If civilization is to advance and man is to reach as yet undreamed of heights he must be free—free to advance, to meet challenge with accomplishment, competition with success.

Sickness, overwork, hunger, poor housing—these are not the real threats to mankind for man can and has in the past overcome them. The real threat is regimentation that stifles the individual and eventually destroys his will to resist. The cost of buying security is amply demonstrated in England. Whether that nation has gone too far down the road to return is a matter of concern to the world. We would suggest that the British people do some soul-searching to determine whether they are not following a philosophy of government that can lead only to disaster.

L. F. Tice

SELMAN WAKSMAN—SCIENTIST, TEACHER AND BENEFACTOR OF MANKIND*

By Randolph T. Major**

WE are meeting here now to honor a great scientist, a great teacher and a great man. All of you know what Dr. Waksman has done. There is nothing that I may say that can add to the lustre of his accomplishments or detract from the honor that is assuredly his due. The many manifestations of the esteem in which he is held that have been showered upon him in recent years: his recent designation as the outstanding citizen of New Jersey for 1948, his election to membership in the National Academy of Sciences and the medals, awards and honorary degrees from many universities and other institutions both here and abroad, which have been bestowed upon him bespeak the honor and regard in which he is held by his fellow men. There are many today who still enjoy the pleasure of life on this earth because Dr. Waksman studied, labored and utilized his scientific ability for the good of mankind.

Perhaps, however, by examining some facets of the life of the man whom we honor today, we shall learn something which may be of value to each one of us and to the civilization of which we are a part.

Dr. Waksman was born in Russia, as have been other great scientists, such as the chemist, Mendeleeff, and the physiologist, Pavlov. But it is true, that great men who have furthered scientific thinking have arisen in many of the countries of the civilized world. The important thing to us is that America opened its doors to Selman Waksman and provided him with the environment and the opportunities which were necessary for the development of his genius. He was born in the town of Priluka, near the great city of Kiev in the heart of the Russian Ukraine. Accordingly, at a very early age he must have been brought into contact with some of the problems of an agricultural region, since it is stated that four-fifths of the population of the Ukraine is engaged in agriculture.

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* Presentation Address for 1949 Research Award by American Pharmaceutical Manufacturers' Association, in Honor of Dr. Selman A. Waksman.

** Vice-President and Scientific Director, Merck & Co., Inc., Rahway, New Jersey.

After graduation from a Gymnasium in the great seaport city of Odessa on the Black Sea, our honored guest emigrated to the United States at the age of twenty-two. During his first few years in this country he lived with relatives on a poultry farm in Metuchen, New Jersey. Again the problems of agriculture and the need for educated people to study them must have been impressed upon his mind. A year after arriving in the United States, Selman Waksman matriculated as a student in the College of Agriculture of Rutgers University with which institution he has been associated, except for a brief interlude, ever since.

At Rutgers, Waksman soon came under the influence of Doctor, later Dean, J. G. Lipman, who stimulated his interest in soil microbiology. How important is the wise counsel and stimulating guidance of a good teacher in the development even of one who later might be looked upon as a genius! I am sure that Dr. Waksman would agree that his early teacher and friend had a profound effect on him in shaping the course of much of his later work.

At Rutgers, Selman Waksman must have been an outstanding student for when he graduated he was elected to Phi Beta Kappa. He has continued to be an outstanding scholar throughout his life.

Waksman was not as young as most men when he graduated from college but this does not appear to have been a disadvantage to him. Was it perchance an advantage? If this was the case, might it not change some of the current educational concepts of our time with respect to the age at which young people should enter college and the age at which they may benefit most from their studies there?

Following graduation from Rutgers he continued his studies there for another year, at the end of which in 1916 he obtained the Master's degree. It is an interesting commentary that the research he carried on during this period was concerned with soil microorganisms, bacteria actinomyces and fungi of the general type with which he has been largely concerned ever since. How fortunate it is that at this early stage in his development Waksman had vision enough to pick a field of endeavor which has been a challenge to him for a lifetime and which has made it possible for him to make so many contributions to society while pursuing those initial leads!

When he had completed the work required for his Master's degree, Waksman decided that he would not follow the accepted

pattern and take a Ph. D. degree in the field of microbiology. Instead he left for the west coast to study under the famous physical chemist, G. N. Lewis, and the biochemist, T. B. Robertson. He realized that an expert knowledge of these phases of chemistry was necessary to him in making progress in his chosen field of microbiology. The degree of Doctor of Philosophy was obtained in 1918.

The need for people with expert training in more than one field of science still exists. Today, however, the time and expense required to become a specialist in any one field is so great that very few young scientists are able to obtain expert training in more than a single field. A committee of the National Research Council recently pointed out to representatives of our organization that one of the greatest needs for funds in support of research today is that for the training of young scientists as specialists in another field than that in which they are already expert. Dr. Waksman realized the necessity for this over thirty years ago.

While in California our friend had an experience which undoubtedly has had an important part in shaping his interest in pharmaceutical and medical problems. During his last year of study at the University of California he worked part-time in the Cutter Laboratories, a member, I believe, of this Association. This experience should be considered another phase of the young man's training which in due time would be put to use. I do not doubt that Dr. Waksman's present awareness of the value to society of cordial cooperation between scientists in universities and in industry stems, at least in part, from this early experience. Might it not be worthwhile as a part of their training for other teachers of science in the universities to obtain some experience in the laboratories of industry in contact with their practical problems?

After receiving his doctor's degree, Dr. Waksman returned to Rutgers and the New Jersey Agricultural Experiment Station with which institution he has been associated ever since—over thirty years of service to what has now become the State University of New Jersey.

In the years 1918 to 1920, Dr. Waksman again came into contact with industry since, during this period, he spent part of his time in carrying on certain investigations of enzymes at the Takamine Laboratories in New York.

In 1921 Dr. Waksman assumed full-time duties at the New Jersey Agricultural Experiment Station and was also appointed Lecturer in Soil Microbiology at Rutgers College. He has continued to serve these institutions full-time since then. In 1929 he was appointed a full Professor at Rutgers.

During this period his reputation in his chosen field of microbiology rose rapidly. He published two books, one on Enzymes with W. C. Davison in 1926 and another entitled "Laboratory Manual of General Microbiology" in 1928 with E. B. Fred, now President of the University of Wisconsin. During this period he published numerous scientific papers on the microbial population of the soil with such titles as, "The Growth of Fungi in the Soil", "The Soil Population", and "Studies of the Metabolism of Actinomycetes". Also, during this period he did much fundamental work on the role of bacteria in the oxidation of sulfur in the soil; also, he did a great deal of work on the relationship between the fertility of the soil and its microbiological population. It was during this period that he published a large number of communications on the decomposition of plant materials in composts and in soil by microorganisms and it was at this time that his outstanding contributions to the knowledge of peat and humus began with such papers appearing as: "Chemical Composition of Peat and the Role of Microorganisms in its Formation", "The Origin and the Nature of the Soil Organic Matter or Soil Humus" and "The Role of Microorganisms in the Formation of Humus in the Soil". Further, he made some fundamental contributions to our knowledge of enzymes during this era.

Dr. Waksman's position in microbiology was recognized in 1931 by the Director of the Wood's Hole Oceanographic Institution who asked him to organize a division of marine bacteriology; he was appointed Marine Bacteriologist at that Institution. Since that time he has spent several weeks of many summers there and has directed a good many investigations in marine bacteriology. Dr. Waksman found, in the course of this work, that bacteria are very much involved in the decomposition of suspended matter in sea water, as well as of dissolved organic substances and organic materials in the surface of the bottom of the sea. He found that the organic matter in the sea bottom mud below the surface bottom layer is similar in nature to soil humus.

Most of us think of the soil as little more than a surface on which we walk or have our lawns, trees and gardens. We may think of a soil as good or bad for lawns or gardens, but little else. Dr. Waksman views the soil as the exciting home of millions of tiny living things—bacteria, fungi, etc., which in themselves make up a large part of the soil and which in turn produce much of the product we know as soil from fallen leaves, dead grass, trees, etc.

In much the same way most of us view sea water as something that looks as though it might be potable, but definitely is not. Or we may view it as a pleasant medium on which to sail or in which to swim or bathe, but Dr. Waksman's studies have shown it has much greater interest than this in its teeming millions of microorganisms which live and have their being in this medium. Dr. Waksman has opened up new vistas for us as we think of or look upon the sea or the soil. What more should we ask of any scientist? But of Dr. Waksman we may say assuredly that his work has accomplished more than this since his studies of the soil have made it possible to explain why crops will grow on certain soils but not on others, and to increase the size of crops obtained by applying to their culture some of the discoveries made by him.

In the same way, his studies of the teeming microbiological life of the sea has made it possible to understand better why barnacles grow on ship's bottoms and to suggest means of preventing this. This is one of the important problems still under investigation at Wood's Hole.

As is evident from what has been said and the number and extent of his publications, Dr. Waksman has not been one to ignore the biblical admonition that one should not hide one's light under a bushel but let it shine before men. His light has shone far and wide. Attracted by his teaching and writings students have come to his laboratory from all over the world, from England, Sweden, Russia, Germany, France, Japan, China and India as well as from many of the States in our Union.

He has surveyed the peat resources of his State of New Jersey and in the summer of 1938 he made a survey of the peat lands of northern Palestine at the request of the agricultural advisory committee of that country. This latter survey was made with a view to the profitable use of these lands for settlement and agricultural operations.

Dr. Waksman is a member of numerous scientific societies and organizations and has been an officer and organizer of meetings of a good many of them, not only in this country but also abroad.

It was quite natural that, when our own organizations became interested in the possibilities of producing chemicals by microbiological action in the latter half of the 1930's, we should turn to our neighbor in New Brunswick, Dr. Waksman, for advice. A fellowship was established in his department for the study of the synthesis of chemicals by microbiological action. The first holder of this fellowship, a student of Dr. Waksman's, Dr. Jackson Foster, later became the first head of our microbiological laboratory.

New and great interest in the field of microbiology arose in 1939 when Dr. Rene Dubos of the Rockfeller Institute, a former student of Dr. Waksman, announced that he had isolated the antibiotic, Gramicidin, from a bacteria growing in the soil. In isolating this antibiotic, Dubos utilized the so-called enrichment technique used by soil microbiologists which he had learned in Waksman's laboratory. Incidentally, the noun, antibiotic, which is so commonly used today, was coined by Dr. Waksman some time later to designate chemical substances produced by microorganisms which possess marked antibacterial action.

Dr. Waksman recognized immediately the importance that microbiology might have for medicine as a result of these observations of Dubos. Unfortunately, Dubos' new antibiotic did not prove to be too useful a therapeutic agent but shortly thereafter Florey and associates made their epoch-making announcement of the therapeutic activity of the antibiotic, penicillin. As a result of the discovery of penicillin, which proved to be remarkably useful in the control of infections and diseases due to Gram positive microorganisms, Dr. Waksman turned his attention and that of his students toward a search for antibiotics which might be active in the control of infections and diseases due to Gram negative bacteria and to tubercle bacilli against which penicillin was not active. In this study he concentrated his effort on the actinomycetes, a genus of soil microorganism which, over twenty years of study, had demonstrated to him that they were especially promising for the purpose he had in mind. By the fall of 1943 he and one of his students had isolated that life-saver, Streptomycin. They had systematically applied the techniques of soil microbiology that Dr. Waksman had been

studying and developing to the important therapeutic problem before them. The success attained with this new antibiotic was phenomenal but it was only possible as a result of the years of research and patient study that Dr. Waksman had devoted to the microbiological population of the soil.

The rest of the story of Streptomycin is known from one end of the earth to the other and I shall not attempt to say any more about it except that Dr. Waksman in isolating this first cure for that dread scourge of mankind, tuberculosis, has earned the everlasting gratitude of his fellow men. History will no sooner forget him and his work than it will Pasteur, Koch, Lister and the other great men responsible for the development of scientific medicine.

Dr. Waksman's honors have been many. As has been mentioned, he is a member of the National Academy of Sciences. Also he is a corresponding member of the French Academy of Sciences, Swedish Academy of Agriculture, Royal Society of Upsala and the Mexican Society of Natural Science. He is an honorary member of the American Trudeau Society and recipient of the following medals and awards, among others: Passano Award, Emil Christian Hansen Medal from the Carlsberg Laboratory in Denmark, New Jersey Agricultural Society Medal, Lasker Award of the American Public Health Association, the Amory Award of the American Academy of Arts and Sciences, and the John Scott Award of the City of Philadelphia.

Dr. Waksman's publications number some 300 papers and some seven scientific books. But Dr. Waksman has not permitted his work to completely engross him. He and Mrs. Waksman have travelled widely both in this hemisphere and in Europe. Also, they are lovers and connoisseurs of the fine arts including music and the theatre. I must pause at this point to pay tribute to Dr. Waksman's constant companion and stimulant to his flagging spirits, Mrs. Waksman.

In closing, I think we may all agree that the poet Longfellow must have had in mind such people as Dr. Waksman when he wrote:

"Lives of great men all remind us
We can make our lives sublime,
And, departing, leave behind us
Footprints on the sands of time;—

Footprints that perhaps another
Sailing o'er life's solemn main,
A forlorn and shipwrecked brother
Seeing shall take heart again."

It should be noted, however, that although Dr. Waksman has accomplished so much that we may speak in this way of him, fortunately, we may look forward to equal or greater benefits to mankind from the laboratory of our friend in the future. As you know it has recently been announced that from funds received as royalties from the manufacturers of Streptomycin a wonderful new Institute of Microbiology will be erected at Rutgers University for the use of Dr. Waksman and his students. May his labors continue for many long and fruitful years.

ANTIBIOTICS—A PRODUCT OF COLLABORATION BETWEEN UNIVERSITY AND INDUSTRY*

By Dr. Selman A. Waksman

NO other subject, that has originated in the laboratory as a result of academic research, that has found tremendous application in chemotherapy, and that has led to the development of important industries, can be used better for the purpose of illustrating the great potential benefit that may be derived from the close collaboration between the university laboratory and industrial organizations than that of antibiotics.

This particular branch of science did not exist 10 years ago. The very name of this new science was only a dictionary curiosity. To be sure, it was known to the bacteriologists and to a few chemists that certain bacteria and fungi are capable of producing a type of compound which is injurious to the growth of various bacteria, including those causing human, animal and plant diseases. Nobody suspected, however, that here was hidden a treasurehouse of important potential chemotherapeutic agents. It is true that various abortive attempts had been made to utilize such compounds, either in an isolated condition, as in the case of pyocyanase, or in crude culture preparations, as in the case of *Aspergillus fumigatus* cultures, for the treatment of different infections, but these had either been only partially successful or could not be repeated.

Even such a preparation, as penicillin, which was first observed and described in 1929, did not attract any attention on the part of the medical profession, and its potentialities were not recognized even by those few who dared or cared to check Fleming's observations. The primary reasons for this are two: one recognized by Fleming himself, namely the lack of collaboration between the bacteriologist (Fleming) and the chemist (Raistrick), who made in 1932 the first attempt to isolate penicillin); the other which we all recognize at present, the lack of interest among the industrial organizations in these particular laboratory curiosities.

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* Delivered June 9, 1949, at the annual convention of the American Pharmaceutical Manufacturers' Association in Hot Springs, Va.

Credit for first recognizing the tremendous potentialities in this type of compound must go to Dr. Dubos of the Rockefeller Institute for Medical Research. In 1939, he announced the isolation, from the culture of a spore-forming soil bacillus, of two compounds, gramicidin and tyrocidine, which he later designated as tyrothricin. Dubos combined, on the one hand, the training in soil microbiology and microbial physiology and, on the other, the enthusiasm and recognition of the possible utilization of microbial products for combating infectious diseases. He went about it in a rather roundabout way, and what pioneer would not? He enriched a collective soil with a mass culture of collective bacteria and awaited the development of organisms capable of destroying the added bacteria. In due time he succeeded in isolating from the soil, organisms capable of producing substances which had the capacity of destroying bacteria of the type that Dubos added to the soil. Here was an old principle, well recognized in soil microbiology, but in applying it to the solution of a medical problem, Dubos started a new era of scientific research which has touched upon many fields of science, notably microbiology, chemistry, pharmacology and clinical medicine. Most notably it led to the development of new and great industries. This pioneering work branched out at once into 3 distinct pathways:

1. The study of antibiotics of fungi, with the Oxford, England, group in the lead and the penicillins as the major and important products.

2. The study of the antibiotics of bacteria, with the Rockefeller Institute group in the lead, followed by the Columbia, Southern California and other university and industrial laboratories, and leading to the isolation, in addition to tyrothricin, of bacitracin, subtilin, polymyxin and various others.

3. The study of the antibiotics of the actinomycetes, with the Rutgers group in the lead, later followed by other university and industrial laboratories, which resulted in the isolation first of actinomycin, streptothricin, streptomycin and grisein, and later of chloromycetin, aureomycin, neomycin, and others.

It is sufficient to examine the practical progress made in the development of only one representative of each of the above groups of compounds, in order to appreciate the tremendous benefits that have been derived from the close collaboration of the University

laboratory and the Industrial organizations for the benefit not only of those directly concerned, but also of the public at large.

When, soon after the announcement of tyrothricin, namely in 1940, Florey, Chain and their associates at Oxford re-examined the practical potentialities of penicillin, an antibacterial agent produced by a green mold, they were faced immediately with the difficulty not only of producing sufficient amounts for clinical investigations, but also of amounts required for purely chemical studies of the compound involved. Here was a compound that was produced in such infinitesimal amounts (it is to be remembered that the early cultures produced only 2-3 units of penicillin per 1 ml of culture medium as compared to the thousands or so units obtained at present by the manufacturers of penicillin) that many liters were required to give a few milligrams of the preparations. In spite of the fact that all the vessels that could be requisitioned, including urinary receptacles, were put to use, they could produce hardly enough for the treatment of more than 1 or 2 patients.

It is hardly necessary to trace before this audience the further progress of Florey and Chain, their vain appeals to the British industrial organizations, their coming to Canada and finally this country. Fortunately, they were brought in contact with Dr. A. N. Richards, a man of exceptional vision and understanding. He immediately recognized the immensity of the problem involved and because of his high position as chairman of the Committee on Medical Research, succeeded in enlisting the interest not only of Government agencies but also of important American industrial organizations. It is the latter who should receive largely the credit for having solved or at least helped to solve the problem of penicillin, its production, its chemical nature, and its use in numerous infectious diseases.

No effort was spared. Great microbiological divisions were created by organizations which never before dreamt that they would ever have any use for bacteriologists, mycologists or even for microbiologists, the very title of which was known only to very few. Today the name "microbiologists" is a by-word, microbiological societies are being organized and even a Microbiological Institute is being planned.

It is only of academic importance to argue whether most of the credit for the solution of the penicillin problem should go to the

clinicians, as our medical friends seem to think; to the chemists, as my chemical colleagues are fond of arguing; or to the microbiologist, who started it all. It should be emphasized that most important of all, it was the close collaboration of various groups of investigators working in the university and Government laboratories with the industrial organizations, and their staffs of chemists, engineers and other highly qualified experts that made the solution of this difficult problem possible.

It is often said that only a war can stimulate great scientific developments and that only considerable government support may make such achievements possible. Whereas this may have been true, at least to a certain extent, in the solution of the penicillin problem, it certainly did not play any part whatsoever in the solution of the streptomycin problem. The comprehensive investigations in the production of antibiotics by actinomycetes were begun in 1939, before the outbreak of the war. They were carried out systematically without reference to, or one might even say, in spite of, the war. Certainly no Government support was forthcoming, although we actually asked for it. We were told that our investigations were of a purely theoretical nature and offered no immediate practical promise and, therefore, were hardly to be considered on a level that would justify support from Government funds. We did receive some support from one or more philanthropic foundations. The greatest support, however, was given to us by an Industrial organization, whose members were far-sighted enough to appreciate two facts: 1. That without basic research, practical applications will go only so far and no further. 2. Scientific facts are most likely to find immediate practical application when they are channeled into or supported by organizations that understand and are able to bring theoretical facts into practical use.

The great progress of streptomycin is due largely to the collaboration between a group of enthusiastic research workers in a small university laboratory and an industrial group who appreciated the great practical potential of such investigations and were willing to place their staff of chemists, pharmacologists and engineers in helping to solve the practical or applied aspects of these problems.

It was a difficult task, fraught with many failures, but, to the credit of both, no discouragement prevented them from pushing on until the problem was brought to a successful completion. I hope

that none of you will go away with the mistaken impression that one can pull out important antibiotics from one's sleeve. Permit me to tell you the following story. It has been told many times before but will bear repeating.

There is another group that should receive much of the credit in the development of streptomycin, namely Drs. Feldman and Hinshaw of the Mayo Clinic. Their close and untiring collaboration helped considerably in establishing the anti-tuberculosis potential of streptomycin.

The important fact to emphasize, however, is that here was an important problem solved without the help of, or even in spite of, a War and without any support from the Federal Government.

Other antibiotics of actinomycetes, such as chloromycetin, benefited greatly from such close collaboration, notably, the botany group at Yale and the University of Illinois group, the Wisconsin group, with various industrial organizations.

In illustrating the isolation of bacterial products as a result of successful collaboration between a university laboratory and industrial organizations, that of bacitracin comes first to mind. It is through the ingenuity of Dr. Meleney and his associates at Columbia, on the one hand, and of a number of industrial groups, on the other, that the potentialities of this antibiotic could be established. A number of other bacterial antibiotics could be mentioned where such collaboration has been of great benefit in the evaluation of the potentialities of such substances. It is sufficient to mention subtilin and polymyxin in this country and licheniformin and nisin in England.

One could go much further afield and analyze all the other benefits derived from such collaboration, which would involve as nearly a complex relationship as that of modern society itself. It is sufficient merely to mention: 1. the benefits derived from the industry which makes possible further development and extension of the university research program and its training of well-qualified workers; 2. by relieving the industry from the study of some more purely theoretical problems it enables them to concentrate on their more practical exploitation; and 3. by making available to the clinician large quantities of various preparations for clinical experimentation, steps are thus taken for the immediate application of the results from the research laboratory to the medical profession.

Science today, and this is true particularly of biological sciences, requires the close collaboration of investigators from various fields. The microbiologist has to depend on the biochemist, on the organic chemist, on the pharmacologist, the physiologist and finally the clinician to help him in the solution of the many problems in which microbes play an essential role. The close collaboration between the microbiologist and the industrial organizations interested in the utilization of the manifold potentialities of microbes is an absolute requirement, without which little progress can be made.

Microbiology as a science is only now coming into its own. Until now, it has been largely the handmaiden of the pathologist, the agriculturist, and the food technologist. In becoming an independent discipline, microbiology has much to offer. Only the closest collaboration between the laboratory worker in the university and in the Government laboratory with industry will make possible the most effective utilization by man of the potential activities of those millions of microscopic forms of life inhabiting every substrate around us which still await the inquiring mind.

WILLIAM PROCTER, JR., AND THE PHARMACIST OF TODAY*

By Philip H. Van Itallie **

TO appreciate the work of William Procter, Jr., the "Father of American Pharmacy," one must picture him in the setting of his time.

One hundred and thirty-four years before Procter was born, which was in 1817, Anton van Leeuwenhoek of Holland had perfected the first practical microscope and had first shown the existence of bacteria. However, it was not until Procter was forty years old that Pasteur demonstrated that these same microorganisms were responsible for many of the diseases of plants, animals and man.

The year that Procter opened his first pharmacy in Philadelphia, Robert Koch, the father of bacteriology, was a baby just learning to walk. During Procter's early lifetime organic chemistry was wide-eyed and fragmentary. Bioassay was an unknown art and electricity a mysterious new force evoked by rubbing a cat's fur over a rod of hard rubber. Solid carbon dioxide was a new wonder of a science called pneumatic chemistry.

William Procter, Jr., started his career in pharmacy under the old apprentice system, when a young man, enamored by the atmosphere of the apothecary shop and intrigued by its mysterious devices, was identured or bound in the service of the owner of the establishment for a specified number of years while learning his trade. If a pharmacy school existed nearby and the employer was kind, he might permit his apprentices to attend lectures and demonstrations calculated to amplify what the young man was able to learn from his employer. But colleges of pharmacy were a new-fangled institution and there were no rules or laws to control the practice of either medicine or pharmacy.

At a time when all a man had to do was to call himself a pharmacist, to be a pharmacist, Procter helped lay the foundations of scientific pharmacy as we know it today.

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* Address delivered at the College of Pharmacy, University of Toledo, April 27, 1949, at the unveiling of a group of pictures reproduced from Wyeth paintings, known collectively as "Pioneers of American Medicine."

** Technical Editor, Wyeth Inc., Philadelphia, Pa.

There are good reasons why we call William Procter, Jr., the "Father of American Pharmacy":

He contributed more than five hundred monographs on the production, standardization and testing of drug preparations. These monographs were the result of Procter's own original work in the laboratory. The list of his papers embraces practically all substances known in his day; the majority were botanicals.

Several years after completing a two years' course of study at the Philadelphia College of Pharmacy—oldest pharmacy school in America—Procter became Professor of Pharmacy at that institution. He was the first pharmacist to be so honored; previously all instruction had been given by physicians.

Procter helped found the American Pharmaceutical Association and, as a very active member, labored indefatigably in the interests of professional pharmacy; he attended every meeting and was a member of many of its committees.

He was an inspiring teacher and was for twenty-eight years an editor of the American Journal of Pharmacy, a publication which began in 1821 and has since been published regularly by the Philadelphia College of Pharmacy. During most of these years he also ran a successful retail pharmacy. To all these tasks he brought to bear the stern principles of his Quaker upbringing.

His father, a Yorkshireman, was a carpenter by training but made his living as a hardware dealer in Baltimore. Isaac Procter was the descendent of a family of Quakers. Possessed of little education or financial advantages, he emigrated to this country in 1793, when Washington was President of the United States. Yellow fever was raging in Philadelphia and the good ship William Penn was detained in quarantine, obliging Isaac Procter and his fellow passengers to land at Gloucester, New Jersey, where they crossed the Delaware and, skirting Philadelphia, stopped on the first day to attend a Friends' meeting at Fallsington, Pa. Here he met the Quaker maiden, Rebecca Farquhar, whom he married six years later in the same meeting house.

William Procter, Jr., was born in 1817, the ninth child of this marriage. When he was but three years old, his father died. Straitened family circumstances forced young William to leave school at an early age to earn a few pennies in a copper shop. This, however, was not an unmixed evil for here Procter acquired an

early dexterity with tools which later enabled him to build percolators and other pharmaceutical equipment.

William's mother had a lady friend in Philadelphia, Tebitha Turnpenny, to whom she sometimes took her children on a visit. In this way William met Joseph Turnpenny, who was a pharmacist's apprentice in the shop of Henry M. Zollikoffer at Sixth and Pine Streets in Philadelphia. Little did William suspect that this acquaintance was to determine his career, but the sights and smells of Zollikoffer's pharmacy were so congenial to him that, in 1831, when fourteen years old, he entered that store as an apprentice.

Nowadays child labor is rather repugnant to us but young William was thrilled about the mysteries of pharmacy. Evidently Mr. Zollikoffer was no Simon Legree and his young apprentices had plenty of time to study and to learn their trade from the bottom up.

That first day in the apothecary shop was a great event in William's life. He found a huge pewter syringe and one of his fellow apprentices found another one like it; both repaired to the street and drew up a supply of mud from the gutter. With this they squirted each other. According to Procter's biographer, Charles Bullock, this experience gave the "father of American pharmacy" such zest for his chosen field that he "returned to the store, laid away his syringe, and took from the shelf a copy of Henry's Chemistry, remarking, 'This is just what I like' ". So it seems, George Washington had his little hatchet, and William Procter had his syringe.

For five years, Procter quietly pursued his duties as an apprentice, living in with the family of Mr. Zollikoffer and, according to Bullock, "endearing himself to all by his cheerfulness, brightness and alacrity in all his duties."

In March, 1837, one year after the death of his mother, he successfully passed his examination as a candidate for a diploma from the Philadelphia College of Pharmacy, having completed a highly meritorious thesis on *Lobelia inflata*, in which he demonstrated the presence of the alkaloid, lobeline, which is the active ingredient of this plant.

In May, 1840, when he was 23 years old, Procter was elected a resident member of the College, and from that period onward we

find the volumes of the American Journal of Pharmacy containing many contributions from his pen.

Many a pharmacist of his day would have considered his education complete at this point, but William was never satisfied and, by diligent reading and studying he absorbed all that could be learned about the subjects kindred to his profession. He arose early in the morning and spent several hours each day studying such textbooks as then existed: Turner's Chemistry, Ure's Dictionary, and Dalton's Chemistry. He continued in the employ of Henry Zollikoffer and, while there, found time to do experiments in basic chemistry.

Electricity, galvanism and electromagnetism were fascinating to Procter, at a time when Davy and Faraday were laying the foundations of modern electrical science. Procter attended graduate lectures given by Dr. Hare on electricity, and by Dr. Mitchell on the solidification of carbon dioxide. He constructed an electromagnet and made a blow pipe so that he could fashion his own glass apparatus.

He renewed his engagement with Mr. Zollikoffer and in 1841 was honered by being elected secretary of the Committee on Revision of the U. S. Pharmacopeia. In this capacity he had further opportunities for research; this involved the production of ether and Hoffman's anodyne (Spirit of Ether Compound).

In 1844, when he was 27 years old, he purchased a property at Ninth and Lombard, one block from Zollikoffer's store, in which he opened his own apothecary shop, a few months later. Procter's modest shop was surrounded by many empty lots and the neighborhood was not of the best. Nearby, beyond what were then the city limits, gangs of hoodlums were on the prowl. In a more dignified manner, Procter's biographer described these as "unrestrained rings of lawless associations." The neighborhood did not encourage prosperous folks to trade there and Procter lamented, in his diary, "the anxiety incident to opening a new store" and the burdens of unemployment.

A modern "live wire" might have disposed his mind to merchandising but Procter spent his idle time improving many of the formulae in the pharmacopeia and devising new preparations. Having no family to support, Procter needed little money and, deep down in his Quaker soul, he believed that "the Lord will provide."

Procter's faith was to be rewarded. The new police commissioner did a bit of gang busting and made Procter's neighborhood a fit place for substantial citizens to live. Business picked up.

In 1847, Procter made his introductory address as a full professor of pharmacy at the Philadelphia College of Pharmacy; in this lecture he expressed the view that only students morally and intellectually prepared for the profession of pharmacy should enter pharmacy schools. He particularly reproached parents and guardians who burdened the profession with students and apprentices who would be much better advised to embrace other careers.

At the age of 32, Procter married Margaretta Bullock. By this time he had become a leader in pharmacy of outstanding reputation.

In 1851, Procter was one of three delegates from the Philadelphia College of Pharmacy to attend a meeting in New York, called by the New York College of Pharmacy to consider laws relating to the inspection of drugs and the fixing of standards. This convention was impressed with the advantages that would result from an association, national in scope, which would be charged with raising the standards of pharmacy. At this meeting a resolution was adopted to call a convention to be held in Philadelphia in October, 1852; at that convention the American Pharmaceutical Association was formed.

Throughout his adult life Procter taught, experimented, wrote, and maintained an active and highly respected pharmacy. An ether explosion which rocked his store and blew out the plateglass windows brought to a head a plan for the enlargement of Procter's store. He constantly expanded his manufacturing operations and made every drug in the pharmacopeia, as well as many unofficial preparations. At one time he made relatively large quantities of reduced iron which, as Quevenne's Iron, was popular as a hematinic; later he produced pepsin in quantity, since the commercial grade of this product was not good enough to meet Procter's uncompromising standards.

In those days there were no effective laws to regulate the manufacture of drugs. Adulterated botanicals and chemicals flooded the market and the conscientious pharmacist had to test any drugs he bought very carefully if he wanted to be sure that the tinctures and fluidextracts he made from them would be of the required strength and efficacy.

Chemical analysis permitted him to test the purity of many inorganic preparations but when it came to botanicals and their extracts there was often no way to test their strength. The best assurance the doctor or his patient had of obtaining a medicine of the correct composition was to go to a reputable apothecary who knew enough pharmacognosy to recognize a pure drug when he saw one, and who could be relied upon to supply galenical preparations which were correctly and freshly prepared.

The mid-nineteenth century saw the rise of the manufacturing pharmacist, the outgrowth of the laboratory of the individual apothecary. Those of us who are familiar with the background of the Food and Drug Act of 1906 appreciate the chaotic conditions which prevailed before the late Dr. Harvey W. Wiley made his famous crusade which enlisted the aid of President Theodore Roosevelt and resulted in the enactment of legislation that had been urged unsuccessfully for sixty years.

The earliest law designed to stamp out adulteration of foods and drugs was the Edwards Act of 1848. Procter had a great deal to do with the drive which led to the enactment of this law which prohibited the importation of adulterated drugs. More adequate regulation of drug production had to await a more enlightened and advanced era than that in which Procter lived. Bacteriological methods and biological assays had to be developed before it became possible to prove the purity and strength of many drugs. Science had not yet advanced to the point where legal tests could be devised to make pure drug laws enforceable. Under the circumstances, one had to depend on the integrity of the individual. There were reputable manufacturers but there were also others who operated without a conscience.

Procter, the honest apothecary, found himself in competition with men who made worse drugs for less—and in large quantities. In an address before the American Pharmaceutical Association in 1858, Procter spoke his mind:

> "It is well known that vegetable extracts, fluidextracts, pills of all the official formulae, plasters, cerates, compound powders, in fact nearly all the empirical organic preparations of any note are now made by various large manufacturing establishments. The formulae employed by these makers do not

agree with each other, nor are they generally in accordance with the pharmacopeia, either as regards medicinal strength or manipulation.

"With variable degrees of conscientiousness as regards the efficiency of preparations; and with varying knowledge and skill to effect the manipulations required . . . it is as rivals for a market, and in the competition which follows, that the most serious evils arise. . . . These gentlemen, like other manufacturers, take all the means considered usual or honorable in creating a market. They do not wait until the slow and deliberate footsteps of the therapeutist, and his apothecary, have developed the value of remedies and created a demand for them; but instantly on their announcement in the journals and most often before their performance is demonstrated, quantities are disseminated over the country and vended by parties unacquainted with their merits, or kept in store by druggists as agents until the process of deterioration renders them more or less worthless.

"There are many preparations which may be advantageously made on a large scale, or which, owing to the nature of the material or apparatus used, may be better made in one locality than in another; but such are the exceptions, not the rule. It certainly should be the pride, as it is the duty of the pharmaceutist, to make for himself all those important, though often not permanent, preparations which are termed galenical, as well as many chemical substances. . . .

"How easily may a worthless extract be palmed off on the apothecary, and how utterly impossible, from known data, often is it, for a tincture or fluidextract to be detected when of deficient strength, or when prepared from drugs of inferior quality. . . .

"Pharmacy may be defined as the art of preparing and dispensing medicines, and embodies the knowledge and skill requisite to carry them out in practice. But if the preparation of medicines is taken away from the apothecary and he becomes merely the dispenser of them, his business is shorn of half its dignity and importance, and he relapses into a simple shopkeeper. How can an apothecary properly educate his appren-

tices, unless he affords to them the opportunity to make the medicines they dispense?"

Procter wound up his address by assuring any drug manufacturers in his audience that his remarks were not moved by the slightest degree of personal feeling against them. He urged the following remedies for the evil as he saw it:

"First, we should insist on the clear and distinct annunciation by manufacturers of the proportional strength of preparations and the processes employed. . . .

"Secondly, the Association should use its best endeavors to compel the adoption of uniform strength and formulae for all standard preparations not in the pharmacopeia, and an adherence to the processes of that authority for those that are found in it, and

"Thirdly, to use efficient means to get the next edition of the pharmacopeia to include all those preparations of worth which are now known and used as unofficial preparations."

Well, Mr. Procter, almost 100 years have gone by since you made your speech in Boston. History does not record what, if anything, the pharmaceutical manufacturers at this meeting had to say in rebuttal. But probably it was not very much, because at the time, even the best defense could not have been too convincing.

Permit us to bring you up to date on what has happened in the past 100 years. The U. S. P., to which you devoted such unstinted efforts is as important today as it ever was. In 1888, fourteen years after your death, a companion volume, the National Formulary, appeared for the standardization of important formulae not covered by the U. S. P.

The legislative control which you demanded has been provided beyond your wildest dreams and today, not only all official preparations, but all other drugs as well, are subject to the closest governmental scrutiny. We have laws to control the advertising of manufacturers and today, if you look at the legend on a drug label, or the claims in circulars and in advertising, you can be pretty sure that what you read is the truth.

As to the deterioration of manufactured drug products, this problem has been largely overcome by the greater scientific control

which can now be exercised over production. Most drugs will now keep indefinitely, and those that do not are plainly labeled with an expiration date which protects the consumer. Due to the severe control now being exercised over drug production, medicines made by manufacturers are subject to many tests before they are released on the market.

If you had any idea that these control measures would keep the manufacture of drugs in the laboratory of the retail pharamcist, you have a great surprise in store for you. Perhaps it will disappoint you to hear that the preparation of basic drugs has been taken almost totally out of the hands of the apothecary on the corner. When you said that this would reduce the status of the apothecary to that of a "mere dispenser of drugs", you were partially right—though the corner druggist of today has many duties and responsibilities which would surprise you.

If you had your life to live over again, you would from the start be attracted to the research end of pharmacy, which has become a function exercised almost wholly by manufacturing establishments, and to a small extent by scientists attached to educational institutions.

Even today, Mr. Procter, we have good pharmacists teaching in schools of pharmacy, and often continuing successful retail establishments. As one of today's educators, Dr. Ivor Griffith, President of your old Alma Mater, pointed out recently, you were not only the father of American Pharmacy, but even more surely the father of American pharmaceutical research.

During the past 100 years, enormous progress has been made in medicine and in the sciences allied to medicine, including pharmacy, and this progress has been due to men of your turn of mind. You were lucky, Mr. Procter, that you lived in a time when pharmaceutical science had not yet become so complicated that it was impossible for one man to encompass it in its entirety.

Toward the latter part of your life on earth you saw the beginnings of bacteriology and the discovery of the infectious causes of disease. This is now a specialty to which alone some men devote their entire lives. The laboratory of the retail pharmacist would not offer adequate facilities for work of this kind.

The efficacy of drug products has been enormously improved by noting their effects on experimental animals; this work which is

now absolutely vital to pharmaceutical research has no place in the apothecary shop.

The science of organic chemistry has also become an enormously useful tool in the services of pharmacy. You saw the earliest beginnings of the development of this science since you were the contemporary of Berzelius, Dumas, and Liebig. We know you studied the work of these early chemists, but you could not have anticipated the great strides still to be made.

Today, we can duplicate in the laboratory a great many of the active ingredients of drugs produced by nature, and those which we still cannot duplicate we can isolate in pure form from the crude drugs. As a result, the galenical preparations to which you devoted so large a portion of your life are becoming of constantly diminishing importance. To cite a single example, one of the individual glycosides of digitalis, digitoxin, is rapidly making digitalis leaf an article of minor importance, except as a source of digitoxin.

Highly effective organic drugs—some of great complexity—that do not occur in nature have been created in the laboratory out of the dregs of the earth. Some of these are vastly more effective in the healing of disease than the botanical drugs of your day.

Lowly molds have become the source of enormously effective drugs which are likely to extend the span of human life even beyond our allotted three score and ten. Many of the serious diseases of your time are now easily controlled by these drugs extracted from molds.

In addition, many infectious diseases, especially the major infections of childhood, can now be easily prevented and often cured by appropriate manipulation of the very bacteria that cause them and by the use of the serum of animals which have recovered from these infections. The pharmacy on the corner would hardly be the proper place for any of these vital operations.

The pharmacist of today, Mr. Procter, must make his choice whether he wants to be a dispenser, or whether he wants to exercise one of the numerous specialized functions now encompassed by pharmaceutical manufacturers. Since your interest was mainly in the laboratory, it is likely that you would prefer to devote your great talents to research in the laboratories of one of our large manufacturing institutions. You would find a great deal of fascinating work still to be done, for men are still dying of the heart disease which

laid you low, and of cancer, and diseases of the arteries, to name but the leading causes of premature death today.

Yet, if your choice fell on the operation of a retail pharmacy, you would find much opportunity for honor and service in this field. The retail pharamacist of today, if he desires to restrict his efforts to professional work alone, can be of enormous assistance to prescribing physicians by his complete knowledge of the thousands of existing drugs and the correct manner in which they should be used.

Perhaps, Mr. Procter, your ghost has observed the many non-pharmaceutical activities in which present day pharmacists are engaging. You may say, "Look here, is this not the very evil of which I spoke in Boston? Are not these pharmacists reduced to the state of shopkeepers?" Well, Mr. Procter, you are a scientist at heart; perhaps these commercial functions are not to your taste, but what is so bad about running a prosperous drug store if that is the way these men's minds are attuned?

The young man who goes to pharmacy school must know that there are many different aspects of pharmacy—all can be honorable and useful. In your day the burden of the education of an apprentice was on the owner of the pharmacy, and you, who received two years of formal college training, were a highly educated man by the standards of your time. Today, the burden of education is almost wholly on the college, and every student receives at least four years of instruction. There are plans to extend the educational span for the pharmacist to six years. All that is left of the apprenticeship of old is the requirement that every student must have completed a certain short period of practical experience.

If there is one thing that you have demonstrated by your life and deeds, Mr. Procter, it is that a pharmacist's education does not end when he graduates from school. The unremitting study and devotion to pharmacy which you exhibited is still as productive of results today as it was when you labored in the shop of Henry M. Zollikoffer in Philadelphia.

Today, our educational facilities are much better and far more convenient and accessible than they were in your time. Today's pharmaceutical graduate, who finds that pharmaceutical research of some specialized character would offer greater opportunity and personal satisfaction than the work of a dispenser and shopkeeper, can find the means of acquiring the requisite knowledge to open the

portals of the laboratory. Other young men are satisfied to make the store their career. Remember, Mr. Procter, your father was a hardware dealer, and he was a respected man in his community.

In our large cities there is a place for a limited number of pharmacies which do an exclusive prescription business, but our modern system of drug distribution is based on the existence of a very large number of commercial pharmacies, in which the prescription department is a limited though important part of the store.

The men who fill prescriptions in these commercial stores are often very good pharmacists—the fact that they also render other profitable services in no way affects the honor and integrity with which they discharge their public health function. It is largely these "part-time" pharmacists who bring the practical results of modern therapeutics to the American people—the poor and the rich, the city dweller and the farmer. It is they to whom thousands of people turn for helpful, common-sense advice.

When you, Mr. Procter, made your introductory address as Professor of Pharmacy at the Philadelphia College of Pharmacy, you urged that only those properly fitted for pharmacy should enter pharmacy school. Your counsel is still good today, but in the intervening century pharmacy has grown—and now pharmacy has room for the prescriptionist, the business man, the pharmacologist, the biochemist, the organic chemist, the immunologist and many others.

The pharmacy school of today cannot hope to do more than to lay the foundation for some of these scientific branches. Its primary object must remain that of training a relatively large number of men to man the nation's corner drug stores. Increasingly the pharmacy schools are equipping these men with the knowledge of practical business matters which will enable them to prosper financially while rendering their public health duties.

The pharmacy schools are furnishing young men of a predominantly scientific bent with the basic background from which they can go on to greater achievements in the specialized sciences. Graduate courses are open to them, leading to Master's and Doctor's degrees.

Formal courses leading to these academic degrees help prepare young men for specialized work in the laboratories of pharmaceutical manufacturers. In the final analysis, however, as you, Mr. Procter,

have proved by your own example, it is the individual student's earnest interest and thirst for scientific truth that lead to personal achievement.

There are today even greater opportunities in pharmacy than existed during your lifetime, Mr. Procter, and you need not feel that the pharmacist has lost his dignity. Rather the pharmacist has split, like the ameba, into many different kinds of pharmacists—a variety to suit every taste from the merchandiser to the Nobel Prize winner.

Mr. Procter—may your spirit of devotion to the progress of pharmacy animate the pharmacists of today. It is fiitting that your likeness should adorn the halls of pharmaceutical learning as an inspiration to us all.

SELECTED ABSTRACTS

Comparative Study of the New Vitamin A Reference Standard. H. A. Ellenberger, N. B. Guerrant, and M. E. Chilcote. *J. Nutrition 37:*185 (1949). The problem of the quantitative analysis of vitamin A has not yet been solved. Various methods of assay have been used but none are entirely satisfactory. Apparently some of the difficulty encountered has been due to variability of the potency of different bottles of the U. S. P. Reference Cod Liver Oil no. 3. Recently this has been replaced with a new U. S. P. Vitamin A Reference Standard, which is crystalline vitamin A acetate dissolved in cottonseed oil. The authors made a study of the relationship between the International Standard (β-carotene), U. S. P. Reference Cod Liver Oil no. 3, the new U. S. P. Reference Standard, and pure crystalline vitamin A acetate.

The factor used in converting physically determined potency data to biological potency has also been a source of confusion. Thus the authors conducted spectrophotometric and biological assays simultaneously on a number of commercial fish oils in order to study conversion factors. The biological assay procedure was essentially that specified by the U. S. P. Vitamin Advisory Board, using rats weighing 40 to 50 Gm. when placed on the vitamin A-deficient diet.

The extinction coefficients at 325 mμ for Reference Oil no. 3 (unsaponified) was 0.817, new Standard 5.25, vitamin A acetate 1520, and for the International Standard at 450 mμ 2300. From the results of the biological assays of the standards certain facts appeared. The new U. S. P. Standard and the International Standard may be considered to be equal in biological potency. The new U. S. P. Standard is 1.36 times as active biologically as the U. S. P. Reference Cod Liver Oil no. 3. Both the spectrophotometric and the biological assay results for the U. S. P. Reference Cod Liver Oil no. 3 were lower than the results reported a few years previously. This indicates that the Standard had lost some of its potency. This loss will also help to account for the variations in assay results as reported in the literature during the interim. Biologically, in terms of the new U. S. P. Standard, the crystalline vitamin A acetate was found to contain 3.045×10^6 U. S. P.

units per Gm. while the U. S. P. Standard no. 3 contained 1250 U. S. P. units per Gm.

Conversion factors for the vitamin A standards and for the various fish oils were calculated by dividing the potency found by bioassay by the $E^{1\%}_{1\,cm.}$ —325 mμ value obtained for the unsaponifiable fraction of the oil when dissolved in isopropanol. Average conversion factors were calculated both arithmetically and logarithmically. Although the U. S. P. Standard no. 3 and the new Standard were originally supposed to be of equal biological potency there is a marked difference between the conversion factors of the oils based on the two standards. This again indicates that the no. 3 has lost about ¼ of its potency. A single conversion factor for all oils, as is often supposed, is not applicable. A wide variation was found between the 27 oils studied. In terms of the new U. S. P. Standard the conversion factors ranged from 840 to 2240 with a logarithmic mean of 1500. In terms of the U. S. P. Standard no. 3 they ranged from 1140 to 3050 with a logarithmic mean of 2040. Several suggestions have been offered as an explanation for the variations in conversion factors for different vitamin A carriers. The inherent errors of biological assay may be contributing factors as may also be interferences of substances in the oils with spectrophotometric measurement. However, in reference to the latter, neither saponification nor chromatography have been found uniformly to reduce the variations. Another explanation offered is that spectrographic data is reliable but that the vitamin A present in various carriers varies in its molecular structure and also in its availability to the test animal. The authors conclude that further investigation is necessary before the biological potencies of all fish oils can be evaluated by physical means.

Alleviation of Experimental Diabetes in Man by the Administration of Reduced Glutathione. J. W. Conn, L. H. Louis, and M. W. Johnston. *Science 109:279* (1949). The administration of purified preparations of pituitary adrenocorticotropic hormone (ACTH) to normal men and women can produce a condition

characterized by sustained glycosuria, hyperglycemia, glucose tolerance curves characteristic of the diabetic state, and relative resistance to the hypoglycemic effect of exogenous insulin. During the administration of ACTH the developing diabetic condition is accompanied by a decreasing concentration of glutathione in the blood. Since there is also a related purine metabolism upheaval the authors suggested that a purine metabolite is responsible for reducing the intracellular availability of free sulfhydryl (-SH) groups which are so necessary for the normal functioning of many enzyme systems. The combination of decreased intracellular concentrations of -SH and increased intracellular concentration of purine metabolites impairs the function of the insulin-producing cells of the pancreas (the product of which is a protein rich in cystine), and also interferes with peripheral glucose utilization by inhibiting the enzyme systems which require free -SH groups.

A metabolic balance study was made upon a normal young man to determine whether or not large amounts of glutathione would reverse an already established hyperglycemia and glycosuria, despite continued administration of ACTH. Renal glycosuria occurred on the first day of ACTH. Hyperglycemia occurred on the second day and continued through the entire period except when glutathione was administered. The reversal of hyperglycemia lasted 1 to 2 hours after each injection of glutathione. There was a sharp elevation of the renal threshold for glucose and a fall of the blood sugar level. It would be expected that a sudden cessation of glycosuria would result in an even higher hyperglycemia were the rate of utilization of glucose not increased or the supply to the blood deceased. Evidence indicated that decreased glyconeogenesis from protein was probably not a factor. Inhibition of hepatic glycogenolysis is a possible explanation of the fall of blood sugar.

Another change resulting from the administration of glutathione was a change in the number and character of circulating white blood cells.

The authors suggest that the changes resulting from the administration of glutathione were due to an improved performance of those systems which require free sulfhydryl groups for their normal function. They suggest, also, that the forces at work in the early stages of the development of human diabetes may be similar to those described in this report.

Properties of an Antibiotic, Circulin. F. J. Murray, P. A. Tetrault, O. W. Kaufmann, H. Koffler, D. H. Peterson, and D. R. Colingsworth. *J. Bact. 57:*305 (1949). An antibiotic which is more active against gram-negative than gram-positive bacteria has been obtained from a strain of bacteria closely resembling *Bacillus circulans.* Thus it has been called Circulin.

The sulfate of circulin was assayed at 2,700 units per mg. It is very soluble in water, less soluble in the lower alcohols, but insoluble in the hydrocarbons. The antibiotic retains its activity when stored at a pH of 2.5 to 6.5 at 4° C. for at least 3 months and is also stable to autoclaving for 15 minutes at 15 pounds pressure in the same pH range. Above a pH of 7.0 its aqueous solutions are less stable.

This antibiotic has a bacterial activity similar to polymyxin and to aerosporin since it is more active against gram-negative than against gram-positive bacteria. In general, however, circulin is less active than aerosporin or polymyxin against gram-negative bacteria but more active against gram-positive bacteria. *In vivo* tests with mice indicated that 10 mg. per Kg. protected against 1,000 lethal doses of *Salmonella typhosa* administered one hour after infection while 16 mg. per Kg. administered immediately after infection protected the mice against 100 lethal doses of *Klebsiella pneumoniae.*

Circulin appears to be less toxic to mice than aerosporin but more toxic than polymyxin. It has an LD_{50} in mice of 150 mg. per Kg. when administered subcutaneously and of 23 mg. per Kg. when given intravenously.

A paper-disk-agar method of assay can be used for the quantitative determination of the antibiotic. This method is essentially the same as the assay method used for polymyxin.

Stability of Penicillin Cream B. P. in Combination With Various Drugs. P. A. Kelly. *Austral. J. Pharm. 30:*304 (1949). The effect on the stability of penicillin in Penicillin Cream B. P. of various drugs which might be prescribed in combination with the cream were studied by the author. The creams were assayed by the agar cup-plate method and each of the added ingredients and the cream base were tested for bactericidal activity. Therefore, any

additional bactericidal activity would be the result of penicillin or the combined action of the penicillin and the added drug.

Penicillin calcium, to the extent of 500 units per Gm., was added to the freshly prepared cream. Tests for stability were conducted on the 1st and the 4th day following preparation. The following drugs were tested in combination in the cream: Boric Acid 10 per cent, Salicylic Acid 2 per cent, Acriflavine 0.1 per cent, Proflavine Sulfate 0.1 per cent, Aminoacridine HCl 0.1 per cent, Mercuric Chloride 0.05 per cent, Ammoniated Mercury and Phenol each 1 per cent, Resorcinol 2 per cent, Ichthammol 5 per cent, and Precipitated Sulfur 10 per cent. The creams were then stored under one of three conditions; A temperature of 60° to 70° F. during the day and 43° to 54° F. during the night, a temperature of 98° F., or in a refrigerator.

It was found that only salicylic acid caused complete inactivation under all three storage conditions. The other drug showed only partial or slight inactivation. However, at the temperature of 98° F. (summer room temperature) only Aminoacridine HCl showed slight inactivation. All of the other drugs showed partial or complete inactivation of the penicillin. Therefore, it would seem that with the exception of salicylic acid the drugs studied cause relatively little inactivation of the penicillin in Penicillin Cream B. P. within four days provided the cream is stored at refrigerator temperature.

Effects of Pasteurization on Survival of Coxiella Burneti in Naturally Infected Milk. R. J. Huebner, W. L. Jellison, M. D. Beck, and F. P. Wilcox. *Public Health Reports 64*:499 (1949). The causative agent of Q Fever, *Coxiella burneti*, had been found to be more resistant to heat than the other rickettsias and most vegetative bacteria. Therefore, since raw milk had been shown to be a carrier for the organism the authors made an investigation to determine whether or not pasteurization eliminated the danger of infection.

Five separate tests were made on milk obtained from two different dairies. Both raw and pasteurized milk was tested by intraperitoneal injection into guinea pigs or mice. Those surviving were then tested by complement fixation tests to ascertain whether or not antibodies against Q Fever had been developed in the test

animals. Of 52 guinea pigs injected with raw milk 92.3 per cent were positive in the complement fixation test. All 36 animals injected with milk pasteurized by the high temperature short time method were negative while 3 of 48 guinea pigs injected with vat pasteurized milk were positive. The latter 3 positive tests were all in one experiment.

From these experiments it would appear that the holding vat method of pasteurization is not entirely successful in eliminating *C. burneti* from milk. The pasteurized milk tested in each case was the same milk also tested in the raw state before pasteurization.

Experimental and Clinical Effect of Aureomycin on Pertussis. J. A. Bell, M. Pittman, and B. J. Olson. *Public Health Reports 64*:589 (1949). Pertussis has proven to be resistant to all methods of treatment which are suitable for general use in the home. However, the authors found the experimental effectiveness of aureomycin against pertussis so promising that clinical trial was instituted.

Experimental studies were made on white mice infected by intracerebral inoculation of 0.03 cc. of a suspension of a culture of *Hemophilus pertussis*. For treatment the aureomycin was injected subcutaneously in a total treatment of 0.078 to 32.0 mg. of the antibiotic. The frequency of treatment varied from 1 to 4 times a day, the duration of treatment from 1 dose to 8 days of treatment, and the interval between injection of the culture and the beginning of treatment from 6 to 96 hours. The results from these experiments indicated that treatment beginning 48 hours after infection was more effective than treatment begun at any other time. Apparently a single dose of 10.0 mg. of the drug approached the toxic level in infected mice but not for non-infected mice. In general, a treatment regime of small doses given at frequent intervals over a period of several days delayed and prevented deaths more effectively than larger doses given singly or at frequent intervals for a few days.

A preliminary trial in 20 cases of pertussis when compared with 380 control cases suggested that aureomycin shortened the clinical course of the disease. There was a gradual but prompt reduction in the frequency of paroxysms in the treated cases following the institution of treatment. The most favorable results occurred in those

children treated early in the course of the disease. The dosage employed was a total of 0.5 Gm. of aureomycin per Kg. of body weight given orally in divided doses over a period of 8 days. No untoward effects resulted from treatment. Whenever vomiting occurred immediately after treatment the dose was repeated.

The Topical Use of Vioform in Dermatology. I. Martin-Scott. *Brit. Med. J.* No. 4610:837 (1949). A total of 115 cases of various skin diseases was treated with Vioform (5-chloro-7-iodo-8-hydroxyquinoline) in the form of a 3 per cent washable-base cream and in a 3 per cent petrolatum ointment. The dermatoses had been of varying time standing and most of the cases had been treated with a variety of preparations.

There were only 2 failures in 15 cases of sycosis barbae, none in 17 cases of folliculitis of other areas, in 10 cases of post-auricular dermatitis and 5 out of 10 cases of acne vulgaris. The crusting and inflammation subsided in all of 14 cases of secondarily infected eczema but the underlying eczema was cured in only 2 cases. Good results were also obtained in a variety of other dermatoses, including angular stomatitis, internatal intertrigo, chronic perionychia, septic excoriations, pustular epidermophytosis, herpes zoster, and pemphigus vulgaris. No improvement was noted in cases of chronic lichen simplex, pruritus ani, nor furfuraceous impetigo.

The preparations were found to be relatively non-irritating. Only about 5 per cent of the patients admitted that there was a slight stinging of short duration when the preparation was first applied. No systemic toxic effects due to absorption through the skin were encountered.

The only disadvantage that manifest itself was the yellowish-grey color. The cream was readily removed from fabrics but the ointment was removed with difficulty.

The mode of action of Vioform was previously thought to be due to the liberation of free iodine. However, animal experiments previously reported failed to support this theory. The author also reported the case of a patient who was extremely sensitive to iodine. This patient developed extensive vesticular eruption to a patch test with mild iodine tincture but no reaction after 48 hour contact with the 3 per cent Vioform ointment.

BOOK REVIEWS

To the Lilacs—A Book of Optimism. By Ivor Griffith, Ph. M., Sc. D., F. R. S. A. 270 pages. International Printing Co., Philadelphia, Pa. Price $4.00.

The majority of our readers remember well the many articles and editorials written by the former editor of this Journal, Dr. Ivor Griffith. His keen insight into human affairs and frailities coupled with his Welsh wit and flavor have brought him considerable renown as a speaker and author, not only in the field of pharmacy but throughout broad areas of American life.

"To the Lilacs", like his former book "Lobscows" is a collection of some sixty short articles: parts of addresses and poems culled from his thousands of articles and addresses over the past decade. Each one makes a point and drives home a lesson, but there is always that sense of humor or that Welsh note of sadness that have made Dr. Griffith's talks long and well remembered. As representative of the contents a few of these articles are cited: "Dr. David Roberts—Upstairs", "Who's Important", "The Pedagogic Rebel", "Song of the Canary", "Lament", "A Christmas Prayer", "Citizenship", "Education for Leisure As Well As for Labor", "Monumental Mistakes" and "Education Begins at Home".

As the book's title indicates this is a book of optimism and not one that leaves the reader depressed and confused as seems to be the popular trend in today's literature. "To the Lilacs", itself, is a title which has as its source a small sign almost hidden in the park but seen and read one dreary, bleak, winter morning by the author, whom it gave faith and promise of spring.

Those who enjoy reading books that leave them with a sense of futility and utter depression will not enjoy this sparkling compilation. On the other hand, those who find a joy in living, who love their fellowman and see in life an exciting challenge and experience—they will find this book, as many know the author, entertaining and thought-provoking; an epitome of the brighter side of life but with a quiet reminder of the purpose and meaning of man's existence.

L. F. TICE

A Textbook of Colloid Chemistry. By Harry Boyer Weiser. Second Edition. x + 444 pages, 117 figures. John Wiley and Sons, Inc., New York. Price $5.50.

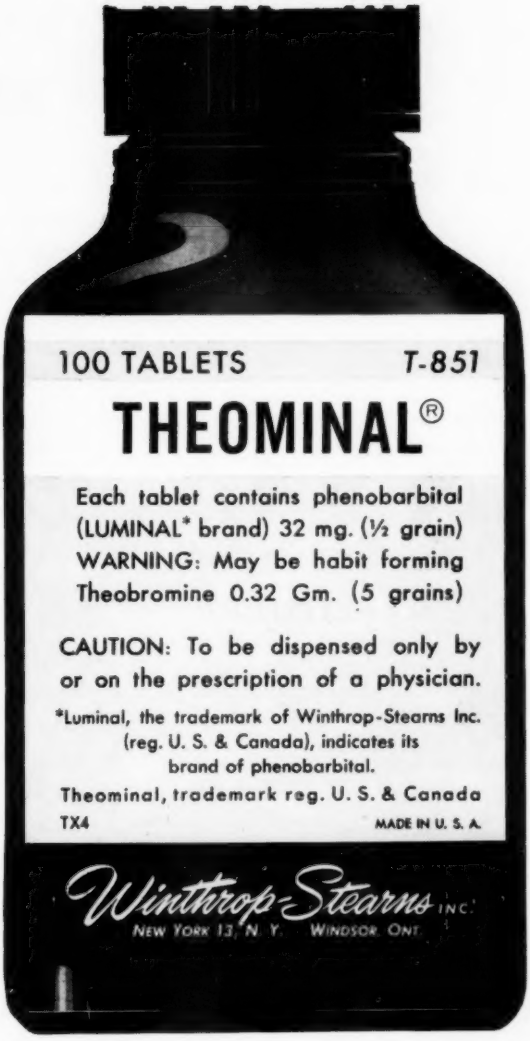
This is the second edition of a well known text on colloid chemistry. After an introductory chapter, Part 1 (Chapters 2 to 8) deals with Adsorption; Part 2 (Chapters 9 to 18) discusses Sols; Part 3 (Chapters 19 to 20) is on the subject of Gels; Part 4 (Chapters 21 and 22) describes the properties of Emulsions and Foams; Part 5 (Chapters 23 and 24) is on Aerosols and Solid Sols; and Part 6 (Chapters 25 and 26) describes the applications of colloid chemical principles to Contact Catalysis and Dyeing. An author and subject index follow.

The book has not been extensively altered in this revision. In general, the organization is the same, except that references are now collected at the end of the chapter. The changes in subject matter comprise mainly the inclusion of more applications of colloid science to allied fields and to industry.

Not many typographical errors were noticed. These were found on pages 173 and 274 (where, apparently, a phrase is mistakenly repeated). An error which is especially annoying to one who has used the book as a text appears on page 125 and in figure 33. This error, which occurs in the derivation of an expression for the spreading coefficient, was present in the first edition, but corrected in a later printing. The text and figure in the second edition now repeat this error.

The book is recommended for the usual college course in colloid chemistry. It covers the field adequately, and should stimulate a real interest on the part of the student who uses it.

LOUIS A. REBER



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